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Review

Pesticides and the Gut Microbiota: Implications for Parkinson's Disease

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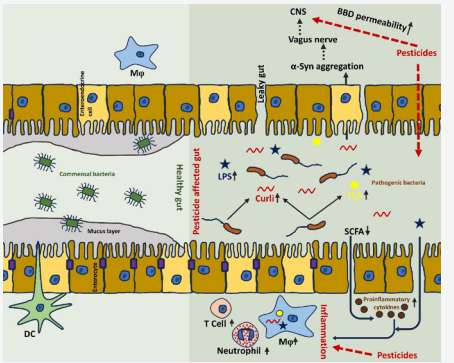
ABSTRACT: Parkinson's disease (PD) affects more people worldwide than just aging alone can explain. This is likely due to environmental influences, genetic makeup, and changes in daily habits. The disease develops in a complex way, with movement problems caused by Lewy bodies and the loss of dopamine-producing neurons. Some research suggests Lewy bodies might start in the gut, hinting at a connection between these structures and gut health in PD patients. These patients often have different gut bacteria and metabolites. Pesticides are known to increase the risk of PD, with evidence showing they harm more than just dopamine neurons. Long-term exposure to pesticides in food might affect the gut barrier, gut bacteria, and the blood−brain barrier, but the exact link is still unknown. This review looks at how pesticides and gut bacteria separately influence PD development and progression, highlighting the harmful effects of pesticides and changes in gut bacteria. We have examined the interaction between pesticides and gut bacteria in PD patients, summarizing how pesticides cause imbalances in gut bacteria, the resulting changes, and their overall effects on the PD prognosis.



1. INTRODUCTION

Parkinson's disease (PD) is one of the most prevalent neurodegenerative conditions worldwide, second only to Alzheimer's, and affects approximately 5% of people above the age of 65.[1] According to the World Health Organization (WHO), the incidence of PD has doubled in the past 25 years, reaching more than 8.5 million cases globally in 2019.[2,3] During the same year, PD caused 5.8 million disability-adjusted life years (DALYs), an 81% upsurge since 2000, and resulted in 329 000 deaths, more than doubling since 2000.[2,4,5] This manifold rate of increase in PD occurrence is a matter of grave concern and has driven research toward the reasons behind the development of sporadic PD. Thousands of studies in this field have specified that lifestyle changes and environmental factors are mutually responsible for PD etiology. Among environmental factors, contact with pesticides has long been known to be related to PD pathology.[6,7] According to the International Parkinson's and Movement Disorders Society (MDS), exposure to pesticides is considered a distinct risk factor for prodromal PD before the appearance of motor symptoms.[8] In 2012, PD was documented as a professional ailment among French agriculture professionals who have a decade-long history of pesticide exposure.[9] Despite strong epidemiological evidence linking PD to pesticides, global pesticide usage persists at or near peak levels.[10] Significantly, paraquat (PQ), a pesticide affecting the development of PD, has been progressively prohibited in almost 60 nations.[10] However, in countries such as the United States, Australia, India, and Africa, the use of PQ continues.[10]

In spite of the link between insecticides and PD being established, the precise machinery contributing to PD pathology, especially the involvement of ENS, remains elusive.[6,11−14] Recent PD research has focused on the relationship between the gut microbial community and the brain, exploring two-way interaction between the gut and brain, with the vagus nerve playing a pivotal role.[15−17] Recently, the influence of pesticides on gut bacteria has garnered more focus. They can notably alter the microbial community's makeup and activity, possibly playing a key role in the development of PD and other synucleinopathies.[10]

We recognize the substantial research already conducted on environmental exposures, the risk of PD, and the connection between gut microbiota and the brain. However, an integrated approach in which pesticide-induced microbial community alterations play a crucial role in PD pathogenesis is largely lacking. This analysis seeks to unify various viewpoints,

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concentrating on how pesticides influence the gut microbiota and their connection to PD development. This piece will explore the immediate repercussions of pesticide exposure on both the CNS and ENS and will examine their influence on intestinal bacteria and the gut-brain axis, taking into account both localized and widespread dysbiosis. Our study specifically focuses on how pesticide-induced fluctuations in the gut microbial community drive the initiation of PD. Differing from prior studies, which extensively delve into the correlation between pesticides and the interconnectedness of the gut microbial community with the brain in the progression of PD, we delve into the precise mechanisms of these alterations. Additionally, we explore microbiota changes at different stages of Parkinson's progression, offering updated insights and recent research findings.

2. ROLE OF PESTICIDES IN PD PATHOLOGY

The association of environmental toxins, especially pesticides, with PD pathogenesis dates back to the late 1990s when Langston and colleagues reported the intriguing finding of parkinsonism among individuals addicted to heroin. This led to the discovery that MPP^+, an active metabolite of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), is structurally analogous to the PQ, is effective in inducing parkinsonism in human and nonhuman primate PD models.[18] It was proven to be selectively toxic to the dopaminergic neurons of the substantia nigra (SN).[19] Subsequent to this discovery, many agrochemicals have been used to develop PD models (especially rodents and flies), including the herbicides paraquat and glyphosate, the natural pesticide rotenone, the artificial pesticide pyrethroids, the fungicide maneb, and the insecticide dieldrin.[20]

Rotenone, a lipophilic isoflavonoid insecticide, and paraquat, a bipyridyl herbicide, both induce degeneration in dopaminergic neurons through oxidative stress. Rotenone functions through complex I, while paraquat induces its harmful effects via cellular redox cycling.[21] Rotenone hinders complex I in the respiratory chain, leading to selective degeneration of nigrostriatal dopamine, the formation of cytoplasmic inclusions resembling Lewy bodies, and the onset of motor symptoms.[11] PQ^{2+}, which is highly polar, is poor at crossing the blood–brain barrier (BBB). It undergoes redox cycling to form a monocation radical, PQ^+, which appears to act as the agent infiltrating dopamine-producing neurons via the DAT and inducing cytotoxic effects.[22] Exposure to maneb, a dithiocarbamate fungicide, also shows significant toxicity to dopaminergic neurons (both in vitro and in vivo) and causes PD-like symptoms in α-synuclein (α-syn) transgenic mice (A53T).[23] Maneb disrupts pathways associated with PD, those related to tryptophan and phenylalanine metabolism, the synaptic vesicle cycle, dopaminergic synapses, oxidative stress, and mitochondrial function.[24] Compared with exposure to paraquat alone, combined exposure to paraquat and maneb induces dopaminergic cell loss, striatal dopamine depletion, α-syn aggregation, and exaggerated PD-like symptoms in rodents.[25] Exposure to dieldrin, an organochlorine insecticide, causes toxicity to dopaminergic neurons and alters dopaminergic neurotransmission in rodents.[26,27] Dieldrin exposure at different developmental stages alters DNA methylation in genes associated with dopamine neuron development.[28] Glyphosate (Gly), an organophosphorus herbicide, directly harms the central nervous system, leading to neurotransmitter changes and oxidative conditions. It has been linked to toxin-induced PD in cases of both acute accidental and chronic occupational exposures. Its effects on the substantia nigra include alterations in neurotransmitter systems, notably reducing opiate-related dynorphin peptides.[29,30] Pyrethroids, such as deltamethrin, permethrin, or cypermethrin, cause dopamine neurodegeneration through inflammation, oxidative stress, mitochondrial dysfunction, and programmed cell demise.[10] They target ion channels, activate sodium channels, and inhibit GABA receptor-gated chloride channels.[31] Permethrin specifically increases α-syn levels and decreases striatal dopamine.[32,33] In a recent study, ten pesticides were found to have direct toxicity to dopaminergic neurons.[34,35]

Among these, several insecticides, including endosulfan, propargite, dicofol, and naled, are still being used in the United States today.[36] Also, three herbicides-endothall, trifluralin, and diquat-are in use.[36] Additionally, three fungicides, namely folpet and copper sulfate (both basic and pentahydrate forms), remain in use.[3631,32]

Although the cited literature extensively covers the impact of agrochemicals on the nervous system, their effect on the gut microbial community has not been thoroughly investigated until recently.

3. PESTICIDE-INDUCED GUT DYSBIOSIS

A healthy gut microbiota contributes to preserving the integrity of the gut lining and blood–brain barrier, aids in metabolism, and prevents entry and colonization of pathogenic bacteria.[37] Among the 11 categorized phyla, the human gut microbiota stands out for its predominant association with four phyla: Pseudomonadota, Bacillota, Bacteroidota, and Actinomycetota.[38,39] Host genetics minimally influences microbial community composition (<2%) compared to environmental factors, underscoring the importance of the microbial community in assessing the risk of toxic compounds.[40] The gut microbial community holds a vital function in converting xenobiotics into bioactive metabolites, impacting the microbial community and physiology postexposure.[41,42] The interplay between human genetics and the microbial community shapes metabolic pathways, and recent studies have suggested gut bacteria as a possible indicator of chemical exposure, including pesticides.[12,43] Several classes of pesticides have been proven to be detrimental to gut homeostasis, leading to gut dysbiosis over the years.[44]

According to a recent report, a high dose of paraquat in rats dramatically altered the gut bacteria makeup compared to that in paraquat unexposed rats.[45] This study revealed a notable decrease in Phyla Bacillota and Bacteroidota, favoring Phyla Pseudomonadota and Verrucomicrobia, suggesting efficient oxidative stress management postparaquat exposure. Among Pseudomonadota species, *Escherichia coli* (*E. coli*) was dominant postparaquat exposure. *Akkermansia muciniphila*, the second most dominant phylum in the phylum Verrucomicrobia, offers health benefits by potentially adapting to reactive oxygen species and inflammation and enhancing gut barrier integrity through various mechanisms.[46] In adult mice, prolonged contact with a minimal amount of paraquat increased the abundances of Bacillota (family *Lactobacillaceae*), Bacteroidota (family *Bacteroidaceae*), and Verrucomicrobiota (family *Akkermansiaceae*) and decreased the abundances of Bacillota (family *Lachnospiraceae* and *Ruminococcaceae*) and Bacteroidota (family *Prevotellaceae*).[47−50] However, acute low-dose PQ exposure in juvenile mice induced a disturbance in the gut microbiota, showing a highly sex-specific effect, which

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Table 1. List of Altered Bacterial Families and Genera upon Exposure to Different Pesticides[a]

pesticide exposure	change in microbiota			
	increased abundance		decreased abundance	
	Family	*Genus*	*Family*	*Genus*
Paraquat	*Enterobacteriaceae*	*Escherichia coli, Akkermansia muciniphila Lactobacillus, Bacteroides, Parabacteroides, Alloprevotella Helicobacter Gastranaerophilales*	*Rikenellaceae*	*Alistipes, Lachnospira, Coprococcus, Blautia*
	Akkermansiaceae		*Lachnospiraceae, Ruminococcaceae*	*Roseburia, Ruminococcus*
	Lactobacillaceae			
	Bacteroidaceae			
	Prevotellaceae			
	Helicobacteraceae			
	Cyanobacteriaceae			
Rotenone	*Akkermansiaceae, Verrucomicrobiaceae, Desulfovibrionaceae*	*Akkermansia muciniphila Desulfovibrio*	*Helicobacteraceae Rikenellaceae*	*Helicobacter, Alistipes, Lachnospira, Coprococcus, Blautia Roseburia*
Glyphosate	*Coriobacteriaceae*	*Enterorhabdus muris*	*Bifidobacteriaceae*	*Bifidobacterium pseudolongum*
	Clostridiaceae	*Clostridium*	*Lactobacillaceae*	*Lactobacillus* sp.
	Odoribacteraceae	*Butyricimonas virosa*	*Eubacteriaceae*	*Eubacterium plexicaudatum*
	Desulfobacteraceae	*Desulfobacterium*	*Lachnospiraceae*	*Corynebacterium*
			Corynebacteriaceae	*Bacteroides*
			Bacteroidaceae	
Organochlorine pesticides(OCP)	*Verrucomicrobiaceae*	*Akkermansia*	*Clostridiaceae*	*Clostridia, Parabacteroides, Prevotella, Bacteroides*
	Barnesiellaceae	*Barnesiella, Alloprevotella, Oscillibacter, Lactobacillus, Parasutterella, and Escherichia coli*	*Prevotellaceae*	
	Prevotellaceae		*Bacteroidaceae*	
	Oscillospiraceae			
	Lactobacillaceae			
	Sutterellaceae			
	Enterobacteriaceae			
Permethrin	*Enterobacteriaceae*	*Escherichia coli*	*Bacteroidaceae*	*Bacteroides*
	Lactobacillaceae	*Lactobacillus*	*Prevotellaceae*	*Prevotella Porphyromonas*
			Porphyromonadaceae	

[a]In this review, only those pesticides associated with parkinsonism development in different experimental models of PD are considered. The changes listed in this table are the outcomes of various experimental studies in animal models of PD (rodents and primates) and metagenomic analysis of human fecal samples (healthy individuals and PD-affected individuals). The references of the data are given in the main text and the citation list.

was observable only in males. In males, there was an increase in Cyanophyta phylum Cyanobacteria (*Gastranaerophilales*), phylum Campylobacterota (genus *Helicobacter*), and phylum Bacteroidota (genus *Alloprevotella*, *Bacteroides*, *Parabacteroides*), while a decrease was observed in phylum Bacillota, Bacteroidota (genus *Alistipes* and family *Muribaculaceae*), and Bacillota (family*Lachnospiraceae*).[44] Similarly, another study reported significant alterations in the intestinal microbial community of rotenone-treated mice compared to control mice.[51] There were notable changes in specific bacterial taxa, including augmentation of the phylum Verrucomicrobia (genus *Akkermansia)* and declension of the phylum Pseudomonadota.[52] At the family level, in contrast to the control group, the group that received rotenone treatment contained more *Verrucomicrobiaceae* and *Desulfovibrionaceae* and fewer *Helicobacteraceae* and *Rikenellaceae*.[51] A recent study demonstrated that exposure to low doses of glyphosate can alter the gut microbiota, causing a declension in helpful bacteria like *Lactobacillus* sp. (phylum Bacillota) and *Bifidobacterium pseudolongum* (phylum Actinomycetota). It also reduces microbial short-chain fatty acid (SCFA) production, increases fecal pH, and elevates proinflammatory marker levels in exposed mice.[53] Another group of studies reported a reduction in the abundance of the phylum Actinomycetota (*Corynebacterium*), the phylum Bacillota (*Lactobacillus*), and the phylum Bacteroidota in male mice after subchronic and chronic exposure to glyphosate.[54] Another interesting study reported an increase in the abundance of the phyla Actinomycetota (*Enterorhabdus muris*), Bacillota (*Clostridium*), and Bacteroidota (*Butyricimonas virosa*) and a reduction in the prevalence of the phyla Bacillota (*Clostridium tertium*, family *Lachnospiraceae*, and *Eubacterium plexicaudatum*) in pups whose mothers were exposed to glyphosate during pregnancy, indicating transplacental transfer of the pesticide.[55] In another long-term glyphosate exposure study, female mice exhibited an increase in phyla Pseudomonadota and Thermodesulfobacteriota (genus *Desulfobacterium*), while males showed a decrease in the abundance of the phylum Bacteroidota.[56] Multiple studies indicate that organochlorine pesticides (OCPs), including dieldrin, β-hexachlorocyclohexane (β-HCH), and p,p'-dichlorodiphenyldichloroethylene (p,p'-DDE), harm intestinal well-being.[57,58] Exposure of zebrafish to low concentrations of dieldrin for more than 4 months led to a decrease in the prevalence of the phylum Bacillota, a phylum associated with energy absorption. Specifically, at the class level, the quantity of *Clostridia* (Bacillota) and Betaproteobacteria was decreased, along with an upsurge in the abundance of phylum Verrucomicrobia.[59] A different investigation utilizing a rodent framework revealed that lingering exposure to low doses of OCPs can alter the gut microbial community, leading to increased abundances of the phyla Bacillota and Pseudomonadota and decreased abundances of the phyla Bacteroidota,

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Verrucomicrobia, and Actinomycetota. β-HCH, and *p,p′*-DDE notably increased Proteobacteria, especially while reducing Bacteroidia and Bacilli.[60] Similarly, the abundances of *Bacteroides*, *Parabacteroides*, *Clostridium XlVa*, and *Prevotella* were reduced, while the abundances of *Akkermansia*, *Oscillibacter*, *Alloprevotella*, *Lactobacillus*, *Barnesiella*, and *Parasutterella* were increased in the β-*b*-HCH and *p,p′*-DDE exposure groups.[57,60−62] Compared with those in the control group, prolonged postnatal exposure to permethrin, a synthetic pyrethroid, in rats led to a diminution in the richness of *Bacteroides*, *Prevotella*, and *Porphyromonas* species and an increase in the richness of the families *Enterobacteriaceae* and Lactobacillus.[63] Additionally, a recent study reported that the use of fipronil, a broad-spectrum insecticide, harms gut health, potentially driving PD. The protein diaminopimelate converter (DapF) found in *Lactobacillus* and tyrosine carboxylase (TDC) from *Enterococcus* help bacteria maintain normal function and produce metabolites.[64] Simulations of their interaction with Fipronil sulfone (FS) at 92 mg/L for 100 ns showed that FS induced conformational changes in DapF and TDC. These changes could inhibit bacterial function, reduce metabolite production, and potentially influence PD.[65]

The above-mentioned alterations in the gut microbiota upon exposure to different pesticides are listed in Table 1. Despite increasing evidence showing gut dysbiosis upon pesticide exposure, the exact role of pesticides in the development of PD remains largely elusive.

4. THE INTERACTION BETWEEN GUT BACTERIA AND THE BRAIN IN PD

Microbes in the gut are crucial for managing digestive and immune activities, impacting how various foods, nutrients, metabolites, and drugs are processed and metabolized.[66−69] The equilibrium of gut microbes has attracted considerable attention due to its significant impact on human health. Imbalances in gut bacteria have been associated with numerous human ailments, such as digestive, brain, metabolic, lung, and heart diseases.[70] Recognized as the central hub in the gut-brain connection, gut microbes are commonly referred to as "the body's second brain".[71,72] The term "microbiota−gut−brain" was coined to describe this intricate and sophisticated system.[72]

Key communication pathways between the gut and brain include the neuroendocrine network, vagus nerve, and hypothalamic-pituitary-adrenal (HPA) axis, with xenobiotics and gut-derived neuromodulators like SCFAs and neurotransmitters (e.g., serotonin and GABA) influencing these interactions.[73] Since Braak proposed the theory that synucleinopathy starts in the gut's enteric nerves and then travels to the cerebrum through the vagus nerve, along with the early gut-related symptoms seen in PD patients, scientists have highlighted the importance of gut bacteria in the development of PD.[74,75] PD can be subdivided into three stages: preclinical (asymptomatic stage), prodromal (nonmotor symptoms manifest), and clinical (motor symptoms manifest). The symptoms of the prodromal stage include constipation, reduced sense of smell (hyposmia), anxiety disorders, depression, cognitive impairment, and potential REM-sleep behavior disorder (RBD), of which constipation is the most common symptom appearing almost 20 years before motor symptoms.[76] Hence, it is obvious that pathological changes in the ENS manifest initially in PD, occurring even beforehand with corresponding alterations in the CNS.[77] Research on both human and animal models with PD has shown damage to neurons and glial cells in the ENS.[78] Studies have found Lewy-type abnormalities and α-syn deposits in deteriorating enteric neurons of PD patients.[79] The experimental introduction of preformed fibrils of α-syn into the duodenum of a mouse model resulted in the disruption of ENS connections and induced temporal gastrointestinal (GI) dysfunction.[80] In people, accumulations of α-syn in GI tissues were found as early as 20 years before being diagnosed with PD.[81] α-Syn deposits in the GI tract can precede Parkinson's diagnosis by up to 20 years. However, our incomplete understanding of α-syn's forms hampers its use as a PD biomarker. In some PD cases, gut inflammation and nerve degeneration may initiate the disease. Environmental pathogens entering the gut can disrupt the nervous system, leading to abnormal α-syn accumulation that may spread to the brain via the vagus nerve.[10,82,83] Recently, the focus has shifted toward host-microbial community crosstalk as a crucial mediator of PD pathogenesis. Research indicates that gut bacteria are essential in forming the blood−brain barrier (BBB) and influencing microglia and astrocyte functions, with reviews highlighting their role in PD risk during early stages and studies showing shifts in gut bacteria composition and subsequent changes in products and metabolites in PD patients[37,84,85,82,34,81]

5. GUT DYSBIOSIS IN PD

The configuration and diversity of the gut microbiota exert a noteworthy influence on diverse functional aspects, including metabolism, barrier integrity, and trophic functions.[86,87] Numerous studies have explored variations in the gut microbial community among individuals with PD in comparison to those without PD.[88] A recent thorough systematic review of 26 studies revealed differences in 53 microbial families and 98 genera between people with PD and those without.[89] However, pesticide exposure is not the sole cause of dysbiosis in PD patients. Several other factors, such as environmental, genetic, and lifestyle factors, play pivotal roles in gut microbiota alterations in PD patients. The findings across current studies vary significantly, potentially owing to variations in study methodologies, genetic profiles of participants, geographic locations, dietary patterns, lifestyles, health statuses, presence of other medical conditions, and medication usage.[90]

The most frequently observed pattern in PD-related research has been the heightened presence of bacteria from the *Akkermansia* genus, which falls within the *Verrucomicrobiaceae* family. Additionally, other consistent findings include augmented levels of the genera *Lactobacillus* and *Bifidobacterium*, reduced levels of butyrate and SCFA-generating bacteria, which are anti-inflammatory, for instance *Roseburia*, *Faecalibacterium*, *Blautia*, *Coprococcus*, *Lachnospira*, *Fusicatenibacter*, and *Faecalibacterium*; and reduced levels of bacteria from the *Prevotellaceae* and *Lachnospiraceae* families.[91−93] Interestingly, *Bifidobacterium*, *Lactobacillus*, and *Akkermansia* are widely recognized to be "beneficial" bacteria, with the first two genera frequently incorporated into probiotic formulations.[94] The reasons behind their elevated presence in PD patients remain unclear, although they could be attributed to their enhanced ability to thrive in a modified gut environment. It is important to highlight that higher levels of *Akkermansia* have been associated with slow-moving colon transit and reduced body weight and/or fat mass-traits often seen in people with PD.[95−97] Interestingly, PD shows an abundance of opportun-

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istic microbes and inflammation-inducing bacteria, such as *Alistipes*, *Corynebacterium*, *Megasphaera*, *Escherichia*, *Bacteroides*, *Desulfovibrio*, and *Porphyromonas*.[98,99] Studies analyzing metagenomics have uncovered genetic indicators within the intestinal microbial community that reliably distinguish individuals with PD from those who are in good health. A notable portion of these indicators stems from organisms belonging to the *Bacteroides* and *Escherichia* genus.[100]

An elevated presence of certain microbial families, such as *Christensenellaceae* or *Oscillospiraceae*, has been connected to a higher propensity of developing PD, suggesting that explicit shifts in the microbial community could serve as early diagnostic markers for this condition.[101] Imbalance in gut bacteria is noticeable in individuals with early stage PD who have not yet received treatment.[102] Shifts in gut bacteria, similar to those in Parkinson's patients, are seen in individuals with REM sleep behavior disorder (RBD) and their relatives, suggesting early stage changes in PD.[72,103]

Understanding bacterial function at the strain level is vital for understanding the roles of bacteria in PD. However, relying solely on genus and species information might be insufficient. Many genes in the human gut microbial community are still unidentified, limiting our understanding. Despite the identification of numerous species, more than 70% of these species have been characterized. We must not isolate the role of a single microbial taxon but consider it within the broader microbial community context. This entails assessing combined effects, including microorganism interactions and host interactions. Direct assessments of active bacterial metabolic pathways using techniques such as fecal metatranscriptomics, metaproteomics, and metabolite analysis provide a better understanding of how gut bacteria impact wellness and illness.[84]

5.1. Altered Gut Microbiota Entails Stages of Disease Progression in PD. Recent clinical studies suggest that gut bacteria could serve as markers for disease staging, as each stage may present a distinct microbial profile. Gut microbes are linked to various phenotypes of PD, including inception, extent, disease stage, and both nonmotor and motor clinical symptoms.[102,104,105] In PD, nonmotor symptoms, together with RBD, depression, cognitive deficit, hyposmia, constipation, and urinary dysfunction, appear in the prodromal stage and precede motor symptoms (rigidity, akinesia, tremor/nontremor, gait disturbance, and postural instability) for decades.[106,107] Gut microbes may also offer predictive value for identifying individuals at risk of developing PD; for instance, a decrease in the richness of SCFA-producing microbes such as *Fusicatenibacter* and *Faecalibacterium* could indicate a greater likelihood of transitioning to PD in patients with idiopathic RBD.[108] Additionally, a decrease in the microbiota responsible for the production of SCFAs and an upsurge in the richness of proinflammatory bacteria are allied to the severity of cognitive and motor symptoms in individuals with PD.[90,109] A study of 423 individuals newly diagnosed with PD found that GI tissues linked to gut microbiota imbalance might predict cognitive performance.[110] In terms of nonmotor symptoms of prodromal PD, Qian et al. reported that a reduction in Bifidobacterium richness is correlated with depression.[104] Barichella et al. projected a potential association between cognitive decline and increased levels of *Lactobacilli*, along with reduced levels of *Lachnospiraceae*.[111] Additionally, *Blautia*, a genus within the *Lachnospiraceae* family, was observed to be reduced in individuals with mild cognitive impairment, while higher levels of the *Rikenellaceae* and *Ruminococcaceae* families were detected.[109] *Bacteroides fragilis*'s low abundance is linked to a decline in activeness or motivation, while delusions or hallucinations are associated with *Bifidobacterium*.[112] Constipation is documented among the most prevalent GI warning signs, affecting approximately 60% of PD patients.[112] Gut bacteria imbalance in early PD stages can cause digestive issues and constipation, with elevated levels of *Lactobacillaceae*,[113] *Verrucomicrobiaceae*, *Bradyrhizobiaceae*,[114] *Bifidobacterium*, and *Akkermansia*,[115] the latter linked to slower transit and constipation severity.[115−117] The correlation between the changed gut microbial community and the nonmotor symptoms of PD is increasingly recognized, indicating that these findings could lead to further research aimed at understanding the precise processes through which intestinal microbes influence symptoms associated with PD.

Concerning motor signs, the presence of *Lactobacillus* shows a connection with the extent of motor dysfunction, while the abundance of the *Enterobacteriaceae* family and a decrease in *Lachnospiraceae* representation is associated with difficulties in movement, instability in posture, and akinetic-rigid subscore.[111,114,118] Furthermore, specific gut-related pathogens, like *Peptococcus*, *Sphingomonas*, and *Aquabacterium*, have been linked with motor challenges in patients with PD.[104] Distinctive patterns of gut bacteria could distinguish between PD patients with tremors and those without. Among individuals with tremors, there's a prevalence of *Bacteroidia*, *Flavobacterium*, *Roseburia*, *Alcaligenaceae*, and *Propionibacterium*, while *Leptotrichia*, *Akkermansia*, *Clostridium*, and *Verrucomicrobia* are more common in nontremor PD patients.[93,119] In individuals with tremors related to PD, there was a decrease in the prevalence of the *Ruminococcaceae* clan.[120] *Prevotella*, extensively researched as a bacterial marker, shows decreased abundance in PD patients with postural instability and gait issues compared to controls.[114,118] Introducing the gut microbiota from individuals with PD into a PD-transgenic mice model worsens motor symptoms related to introducing microbiota from non-PD individuals.[121] In a longitudinal study spanning three years, a diminished presence of *Roseburia* species in PD patients predicted a swifter progression of both motor and nonmotor symptoms.[122] Several studies have highlighted a connection among the abundance of specific bacterial groups and the duration of PD. Keshavarzian et al. proposed that PD duration is correlated with a rise in the prevalence of the Pseudomonadota division and a decline in the prevalence of Bacillota.[102] These findings discovered an inverse relationship between *Lachnospiraceae* presence and duration of illness.[123] Subsequently, a report says that disease extent influences the intestinal microbiota, with heightened *Lachnospiraceae* level and the coabundant genus *Akkermansia*.[111] Scientists are still investigating the possible link between intestinal microbes and the length of PD. Interestingly, the microbial composition at early disease onset may differ from that at later disease stages. Another independent study observed greater abundances of *Fusobacteria*, *Pasteurellaceae*, and *Alcaligenaceae* in early onset PD patients, while *Anaerotruncus* and *Comamonas* were more prevalent in late-onset PD patients.[124] The distinct gut microbiota profiles associated with disease progression and severity hold promise for opening personalized therapeutic avenues in PD treatment and management.

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Table 2. List of Altered Bacterial Families and Genera Allied to PD Symptoms

symptoms of PD		change in microbiota			
		increased abundance		decreased abundance	
		Family	*Genus*	*Family*	*Genus*
Nonmotor	Constipation	*Lactobacillaceae, Verrucomicrobiaceae, Bradyrhizobiaceae*	*Bifidobacterium, Akkermansia*	Not reported	
	Rapid Eye Movement (REM) sleep disorder	Not reported		*Lachnospiraceae* *Oscillospiraceae*	*Roseburia, Fusicatenibacter, Faecalibacterium*
	Cognitive deficit	*Rikenellaceae, Ruminococcaceae, Lactobacillaceae*	*Alistipes, Ruminococcus, Lactobacillus*	*Lachnospiraceae, Oscillospiraceae*	*Roseburia, Fusicatenibacter, Faecalibacterium*
	Depression and lack of motivation	Not reported		*Bifidobacteriaceae* *Bacteroidaceae*	*Bifidobacterium, Bacteroides*
	Hallucinations and delusions			*Bifidobacteriaceae*	*Bifidobacterium*
Motor	Rigidity/Akinesia	*Enterobacteriaceae*	*Escherichia coli*	*Lachnospiraceae*	*Roseburia*
	Posture/Gait instability	*Enterobacteriaceae, Prevotellaceae*	*Escherichia coli* *Prevotella*	*Lachnospiraceae*	*Roseburia*
	Tremor	*Flavobacteriaceae, Bacteroidaceae, Propionibacteriaceae, Alcaligenaceae*	*Flavobacterium, Bacteroides, Propionibacterium, Alcaligenes*	*Lachnospiraceae* *Ruminococcaceae*	*Roseburia* *Ruminococcus*

The differential abundances of gut bacteria that are associated with nonmotor and motor symptoms in PD patients are listed in Table 2. While various research has linked the clinical features of PD to changed microbial compositions, additional investigations are necessary to offer mechanistic explanations and improve our comprehension of interactions between gut microbiota and the brain.[125]

5.2. Inflammation during Gut Dysbiosis in PD. The GI tract acts as a protective barrier, both physically and immunologically, separating the outside surroundings from the host's internal conditions. The intestinal mucosa lining the GI tract is vital for nutrient absorption because it surrounds the bloodstream, which is semipermeable.[126] Additionally, the body's defense system is essential for preserving the intestinal barrier's integrity.[44] Microorganisms residing in the gut, along with their metabolic byproducts, significantly contribute to compromised intestinal barrier function and increased permeability due to dysbiosis-induced metabolic profile shifts, leading to a "leaky gut" and subsequent inflammation. Dysbiosis disrupts this balance, affecting tight junctions, permeability, and translocation through Peyer's patches.[127] This dysbiosis-induced increase in permeability triggers an inflammatory response in the intestine, resulting in the release of pro-inflammatory signals that could compromise the BBB, inciting neuroinflammation and cell death. Decreased levels of SCFAs, which are crucial for sustaining colonic epithelial integrity, have been associated with this phenomenon.[92] SCFAs also possess immunomodulatory properties, promoting anti-inflammatory responses by enhancing regulatory T cells.[128] Bacteria-generating SCFAs are deemed beneficial to host organisms because of their anti-inflammatory properties within the intestines and their function in maintaining equilibrium between the intestinal tract and the BBB.[129] Therefore, a decrease in bacteria that produce short-chain fatty acids, correlates with increased amounts of fecal inflammatory calprotectin in individuals with PD.[120] The observed diminished abundance of SCFA-producing bacteria among PD patients may contribute to reduced SCFA levels. *Prevotella*, *Faecalibacterium*, *Blautia*, and *Roseburia* have consistently been found to be depleted in PD patients across multiple studies, while *Enterococcaceae* are overrepresented, potentially reducing SCFA production and promoting intestinal inflammation.[117,118,123,126] This reduced presence of SCFA-producing bacteria may further contribute to neuroinflammation, leading to recurrent GI symptoms in PD patients. Furthermore, an increase in *Bifidobacterium* and *Bacteroides* corresponds with heightened quantities of systemic and excremental inflammatory indicators such as TNF-α, neutrophil gelatinase-associated lipocalin, and IFN-γ in individuals experiencing PD.[130]

Phylum Verrucomicrobia (*Akkermansia*) has also been frequently observed in significant numbers in PD patients across various studies.[116,123,131] *Akkermansia* utilizes intestinal mucus as nourishment and transforms it into SCFA acetate, which is essential for synthesizing butyrate, an energy source for gut epithelial cells.[132] Moreover, *Akkermansia* improves mucosal strength and adjusts the immune response. If the gut lining cannot replenish the mucin used by *Akkermansia*, then negative outcomes like inflammation and leaky gut may occur.[126] Besides the noted lack of SCFA-generating microbes with anti-inflammatory benefits in individuals with PD, a higher presence of pro-inflammatory pathogens from the Pseudomonadota phylum has been documented in these patients.[102] The Toll-like receptor 4 (TLR4) signaling pathway, which is responsible for detecting Gram-negative bacterial lipopolysaccharides as well as internally produced molecules from damaged or dead tissues is thought to significantly contribute to inflammation in both the gut and brain related to PD.[133] Dysbiosis may thus contribute to a proinflammatory state, potentially linked to α-synucleinopathy. Dysbiosis and exposure to bacterial endotoxins may induce GI inflammation and increased permeability in PD patients, promoting α-synuclein misfolding.[127] These findings underscore the disruptive effect of dysbiosis on gastrointestinal integrity, triggering an immune response that initiates the neurodegenerative cascade observed in PD.

5.3. Intestinal Rise of the Rare Phylum Thermodesulfobacteriota. As mentioned in the previous sections, a plethora of alterations occur in the gut microbiota composition upon both pesticide exposure and PD-related dysbiosis. While previous research commonly identified alterations in the more prevalent microbiota species, detecting changes in rare species poses a challenge. When the numbers of these infrequent

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species increase, they can have adverse biological effects. According to a comprehensive reanalysis conducted by Romano et al., α diversity of microbiota and the abundance of rare taxa were notably greater in PD samples than in control samples.[92] This implies a decrease in high-abundance species and an increase in low-abundance species. When commensal bacteria multiply to the extent of inducing detrimental biological impacts, they are labeled as pathobionts. For instance, the *Desulfovibrionaceae* family, the predominant sulfate-reducing bacteria in the phylum Thermodesulfobacteriota, typically constitutes a small fraction of the gut microbial community. Under normal conditions, it aids microbial fermentation by converting hydrogen to hydrogen sulfide (H_2S). However, in dysbiosis situations, an increase in sulfate-reducing bacteria, known as a bloom, can occur, causing them to become pathogenic. This increase may impair the intestinal barrier and elevate potentially toxic H_2S levels.[134] The presence of *Desulfovibrio* bacteria links with the seriousness of PD.[98,124] Consequently, PD patients may experience excess H_2S. While H_2S can be beneficial in small quantities, acting as a gaseous neurotransmitter that regulates various body functions, including those in the GI, neuronal, respiratory, cardiovascular, renal, hepatic, and endocrine systems, elevated H_2S levels resulting from a bloom in sulfate-reducing bacteria can become harmful.[135] Such elevated H_2S levels are associated with GI disorders such as ulcerative colitis, irritable bowel syndrome, and Crohn's disease, all of which are linked to an increased risk of PD.[136−139] In another study, through quantitative RT-PCR analyses of fecal samples from 20 PD patients and 20 healthy persons, it was found that *Desulfovibrio* bacteria were hosted in the intestinal microbiota of all PD patients, with these bacteria being more abundant in PD patients than in healthy controls.[140] Apart from producing H_2S, *Desulfovibrio* bacteria are recognized for their production of magnetite (some strains) and lipopolysaccharide, all these are probable elements adding to the clustering and accumulation of the α-syn protein.[98]

5.4. α-Syn Pathology in PD and Its Association with Gut Dysbiosis. Braak's hypothesis suggests that PD starts in the GI tract and spreads to the brain via the enteric and vagus nerves, establishing the gut−brain axis connection. The hypothesis is that misfolded α-syn proteins accumulate in the gut's ENS, travel with the help of the vagus nerve to the CNS, and then spread to other brain regions, contributing to neurodegeneration. Epidemiological studies support this finding by showing a lower PD risk in individuals who have undergone vagotomy.[141] α-Syn is closely linked to PD pathology and naturally regulates gut motility in the GI tract. As mentioned earlier, in PD, α-syn can misfold and aggregate, forming characteristic clumps of insoluble fibrils.[142] Curli, an amyloid protein produced by certain bacteria of the family *Enterobacteriaceae*, such as *E. coli*, is known for its role in biofilm formation. In PD, research suggests that curli may significantly contribute to the initiation and aggregation of α-syn in the GI tract.[143] The colonic mucosal presence of *E. coli* correlates with the deposition of enteric α-syn in PD patients.[144] Preclinical investigations suggest that curli produced by *E. coli* may significantly contribute to the initiation of α-syn aggregation. An overabundance of phylum Pseudomonadota, particularly Gram-negative bacteria, leads to increased *E. coli*, which is known for its curli secretion. Rats subjected to curli-generating *E. coli* displayed elevated neuronal α-syn accumulation in both the intestinal tract and cerebral region, coupled with heightened microglial activation and astroglial activation.[145] This implies that curli, an amyloid protein from gut bacteria, could initiate the process of α-syn aggregation.[146] The importance of curli is underscored by findings that curli expression is crucial for worsening α-syn-induced behavioral deficits in *E. coli*. Additionally, oral administration of a compound targeting amyloid in the intestines halted the hastening of PD-like symptoms and unusual behaviors driven by curli.[147] An alternative research avenue suggests that LPS may contribute to the disease process by accelerating the production of curli fibrils.[148,149] Wang et al. employed comprehensive genetic screening to detect thirty-eight *E. coli* genes.[150] These genes facilitate α-syn-triggered neurodegeneration in PD's *C. elegans*.[150] These genes converge on multiple pathways crucial for bacteria−host interactions in PD. In addition to genes encoding curli, such as csgA and csgB, this study revealed genes involved in LPS production, adenosylcobalamin synthesis, eukaryotic lysozyme inhibition, oxidative stress response, and metabolism. These findings validate previous hypotheses and offer further insights into gut microbiota−brain interactions in PD.[142] Diet-induced gut changes may heighten toxin exposure to enteric neurons. A recent study investigated disease exacerbation in a transgenic PD mouse model resulting from fiber deprivation and exposure to bacterial curli. Examination of the intestinal microbiota, movement patterns, and gut and cerebral disorders revealed alterations induced by both diet and bacterial curli, which worsened motor performance as well as intestinal and brain issues to varying degrees.[151] In a broader context, α-syn has been proposed to interact with both innate and adaptive immunity.[152,153] Inflammation is intricately connected to a cycle that encourages its expansion, a reactive setting boosts α-syn production, misconfiguration, and clumping.[10,154,155] This, in turn, triggers local proinflammatory immune responses.[156] In addition to contributing to inflammation, gut microbes may play an additional mechanistic role in this process. Apart from *Enterobacteria*, some species of *Desulfobacteria* have also recently been reported to play important roles in curli synthesis under altered circumstances, leading to α-syn aggregation.[89] A recent study examined fecal samples from PD patients and their healthy spouses for *Desulfovibrio* species. These strains, when fed to *Caenorhabditis elegans* with human α-syn overexpression, led to increased α-syn aggregates. Confocal microscopy and survival assays revealed increased mortality with *Desulfovibrio* from PD patients, suggesting that *Desulfovibrio* plays a role in PD development by inducing α-syn aggregation. Worms provided *Desulfovibrio* from individuals with PD showed notably increased and larger α-syn accumulations compared to those given bacteria from people in good health or strains of *E. coli*.[157] Additionally, *Desulfovibrio* from PD patients caused significantly greater mortality than did *E. coli* LSR11, indicating their involvement in PD development through α-syn aggregation induction.[158] In individuals with RBD and their close relatives, there are microbial changes resembling early PD, with reduced butyrate-producing bacteria and increased levels of certain bacteria such as *Collinsella* and *Desulfovibrio*. These changes precede the onset of RBD and PD, indicating that the microbial community in the intestines might contribute to the onset of α-synucleinopathy.[159] Moreover, recent research has demonstrated that *Akkermansia* promotes the aggregation of α -syn in the intestines by causing an overload of calcium in intestinal enteroendocrine cells' mitochondria.[160] This theory suggests

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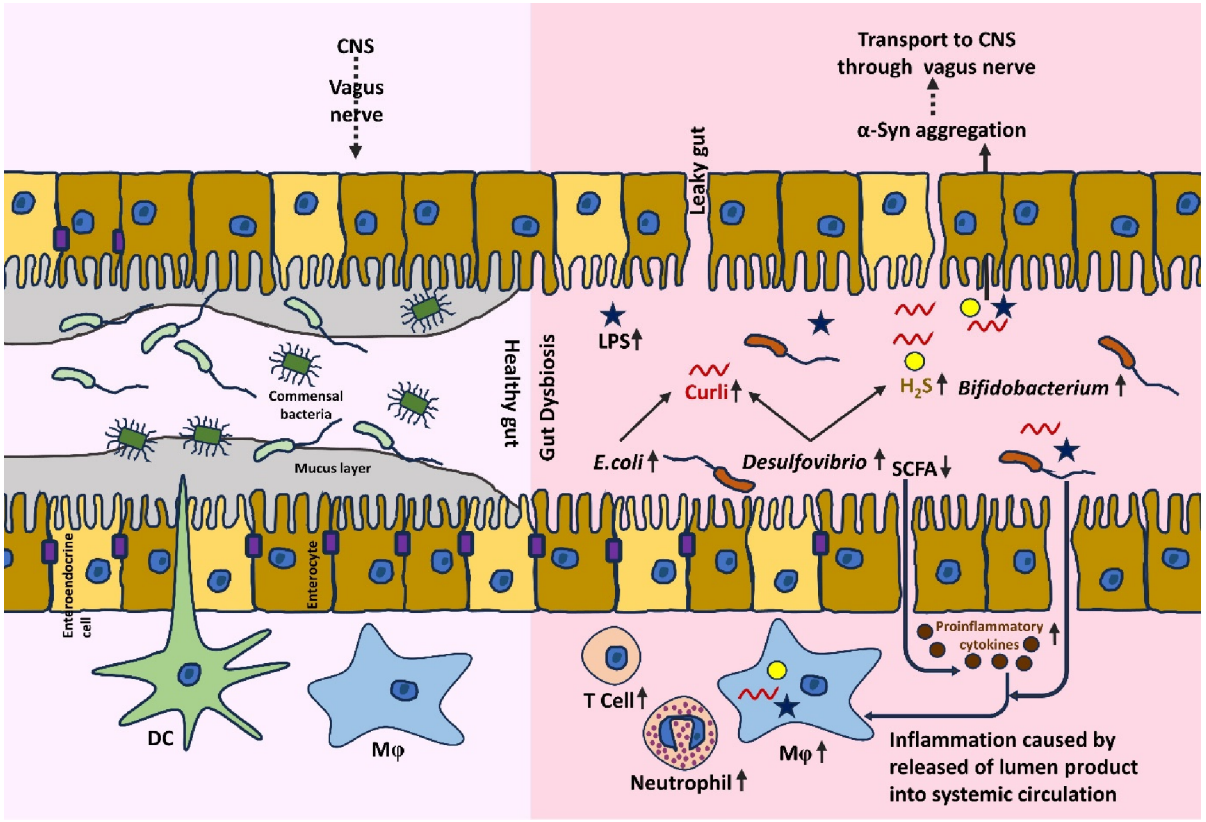

Figure 1. Suggested pathways for gut dysbiosis-triggered α-synuclein (α-syn) accumulation in the intestine and its transfer to the central nervous system (CNS) in PD. Left panel: healthy gut. In a balanced gut, harmonious interactions among microbial communities, epithelial cells, and immune cells are crucial. Right panel: The gut during PD dysbiosis. Dysbiosis reduces SCFA production due to decreased *Roseburia*, *Fusicategnibacter*, *Blautia*, and *Anaerostipes*, while increasing *Lactobacillus*, *Akkermansia*, and *Bifidobacterium* may sensitize T cells. Elevated Gram-negative bacteria increase LPS levels, damaging the intestinal barrier and causing inflammation. The proliferation of sulfate-reducing bacteria (e.g., *Desulfovibrio*) increases H_2S, potentially promoting α-syn aggregation and inflammation. *E. coli*-induced upregulation of the curli protein may modulate α-syn aggregation, possibly leading to its local aggregation in enteroendocrine cells and transport to the brainstem via the vagus nerve. Activation of inflammatory responses increases proinflammatory cytokines, ROS, monocytes, macrophages, and T cells, disrupting the blood–brain barrier (BBB) and allowing pathogenic infiltration into the CNS.

that these cells, believed to be where α-synucleinopathy begins due to external factors, are linked with gut nerves and show a nearby buildup of α-syn proteins.[161] Figure 1 summarizes the mechanism by which altered gut microbiota contribute to intestinal inflammation, leading to the loss of intestinal barrier integrity, a process associated with curli biosynthesis that initiates the aggregation of α-synuclein, subsequently spreading from the intestines to the central nervous system via the vagus nerve network. It is vital to stress that while these findings offer valuable insights into the potential link between curli and α-syn aggregation in the gut, more research is needed to fully grasp this relationship and its relevance to PD in humans.

6. CONCLUSIONS AND FUTURE DIRECTIONS

Pesticide exposure is connected to the onset of PD through disturbances in gut function and alterations in intestinal microbiota. Despite extensive research, the exact role of microbial factors in this connection remains unclear. The increasing global prevalence of PD highlights the need to identify modifiable risk factors that could inform preventive strategies. Historical evidence of PD predating the widespread use of synthetic pesticides and industrial solvents suggests that these chemicals are not the sole cause of PD. Yet, recent epidemiological research has revealed a strong link between prolonged pesticide exposure and higher rates of PD. Reports of PD following acute, high-dose pesticide poisoning and animal studies demonstrating disease onset after pesticide exposure support the notion that pesticides contribute to at least some PD cases. Previously, research often focused on individual risk factors for PD. It is now evident that environmental factors and the way of living, interactions between genetics and the environment, as well as those within environmental factors, are intricate and warrant detailed study. Air pollution, such as that caused by pesticides, has been recognized as a contributing factor to PD through mechanisms including direct neuronal toxicity, systemic inflammation, and gut microbial community alterations. Environmental factors may act synergistically, as shown by the nearly 3-fold increase in PD risk from combined paraquat exposure and traumatic brain injury.[162] The interaction between pesticides and the microbial community is critical. Pesticides and microbial community changes disrupt the intestinal barrier, causing inflammation and microbial byproducts that contribute to α-syn accumulation and neurodegeneration. Research indicates that PD starts in the digestive system with inflammation and the buildup of α-syn. Changes in gut bacteria, particularly *E. coli* and *Desulfovibrio*, are crucial in this context. Several other bacterial families and genera are commonly associated with both pesticide-induced and PD-related gut dysbiosis, indicating a potential link that requires further study. Figure 2

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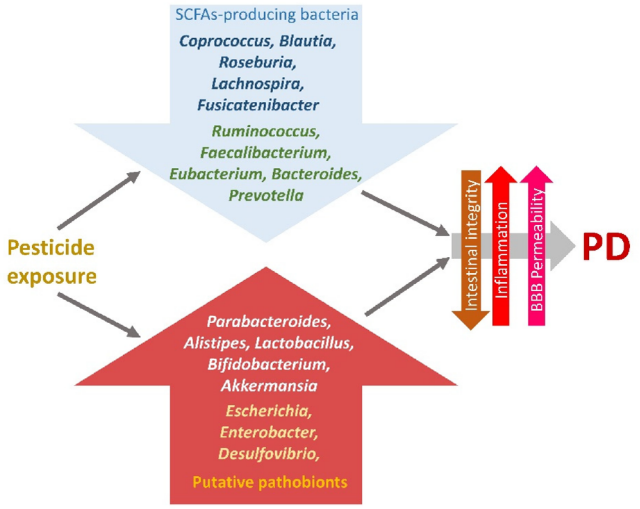

Figure 2. Illustration showing changes caused by pesticides in the gut microbial community and its potential involvement in PD development. Upward arrows depict a rise in the presence of specific bacteria (genus and family) in PD patients versus those without the condition. Downward arrows show a decline in the presence of certain bacteria (genera and family) in PD patients compared to healthy individuals.

summarizes the proposed relationship between pesticide exposure and PD pathogenesis, focusing on alterations in the gut microbial community and intestinal homeostasis. Yet, complexities like genetic vulnerability, indicators of toxin exposure, environmental contamination, gender differences, and the multiomics view of microbial community impacts are still not well comprehended. Despite these uncertainties, there is enough evidence to support preventive measures against the adverse effects of pesticides and gut microbial community imbalance on individuals with PD. The usage of hazardous pesticides has to be minimized and must be altered with benign substitutes, and supplemented with protective equipment. Alternative medicinal or nutritional strategies need to be explored for individuals who cannot evade pesticide contact. Promising microbial community-targeted strategies, including exercise, dietary modifications, phage therapy, pre-, pro-, post-, and antibiotics, fecal microbiota transplantation (FMT), and drugs with small molecular size, offer favorable safety profiles and can benefit both high-risk agricultural workers and the general population. Further research is essential to deepen our understanding of PD pathophysiology and its potential connection with gut dysbiosis. Nonetheless, significant preventive measures can address neurodegeneration and help mitigate the PD epidemic. Through the reduction of harmful exposures and the advocacy of wholesome lifestyle adjustments, we can adeptly navigate this condition, even amidst the absence of disease-altering remedies for PD.

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CRediT: **Nabanita Ghosh** conceptualization, data curation, formal analysis, investigation, project administration, resources, software, validation, writing-original draft, writing-review & editing; **Krishnendu Sinha** software, supervision, visualization, writing-review & editing; **Parames C Sil** supervision.

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